



3-16-01

Patent Docket 17006CON1

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicants: AOKI et al. )  
Serial Number: Pending )  
Filed: Herein )  
For: METHODS FOR TREATING NEUROMUSCULAR )  
DISORDERS WITH BOTULINUM TOXIN )  
TYPES A AND B ) Irvine, California

**PRELIMINARY AMENDMENT**

Commissioner for Patents  
Washington, D.C. 20231

**REMARKS**

**I. Introduction**

This application is a continuation application of application serial number 08/075,048, filed June 10, 1993.

As shown by the attached pages 10-13: claims 1 and 4 have been amended, claims 5-10 have been cancelled and claims 11-19 have been added. The pending claims are therefore claims 1, 4 and 11-19.

**II. The Claimed Invention**

The claimed invention is a method for treating a neuromuscular disorder or condition by administering to a patient a therapeutically effective amount of a botulinum toxin type B (all claims) after the patient has developed either a loss of clinical response to a botulinum toxin type A (claims 1, and 11-15) or has developed neutralizing antibodies to the type A toxin (claims 4, 11 and 16-19).

### III. Amendments to the Specification

The title of the application has been replaced by a title more descriptive of the claimed subject matter and a cross-reference to the parent application has been added after the title. See attached pages 4-9.

### IV. Amendments to the Claims

The amendments to claims 1 and 4 (use of type A toxin followed by use of type B toxin) are supported by at least Example 1 on page 13, and by original claims 2 and 5.

New claim 11 is supported by at least page 1, lines 24-25, page 5, lines 24, and example 2 on page 14-15 of the specification, all of which disclose treatment of cervical dystonia. Note that "cervical dystonia" and "spasmodic torticollis" are synonymous terms.

New claim 12 is supported since treatment of various dystonias, including cervical dystonia, oromandibular dystonia, laryngeal dystonia, lingual dystonia, focal dystonias, and tardive dystonia, is disclosed at at least page 1, lines 24-26, page 2, lines 11-12, and lines 17-18, and page 5, lines 23-35 of the specification.

New claims 13 and 17 are supported by at least page 1, lines 24-25, page 5, lines 24, and example 2 on page 14-15 of the specification, all of which disclose treatment of cervical dystonia.

New claims 14 and 18 are supported by at least Example 2 on pages 14-15 of the specification, which discloses treatment of the cervical dystonia symptom of "abnormal deviations of the head."

New claims 15 and 19 are supported since it was known in the art as of the effective filing date of this application (June 10, 1993) that treatment of cervical dystonia with a botulinum toxin type A can result in alleviation of the pain which accompanies cervical dystonia. See e.g. Jankovic J., et al., *Blepharospasm and oromandibular-laryngeal-cervical dystonia: a controlled trial of botulinum A toxin therapy*, Adv Neurol 50(2);583-91:1988, and Jankovic J., *Botulinum toxin injections in patients with cervical dystonia*, Neurology 39(3) supp 1;294:1989. The abstracts of both these articles are attached.

New claim 16 is supported by at least original claims 4 and 5.

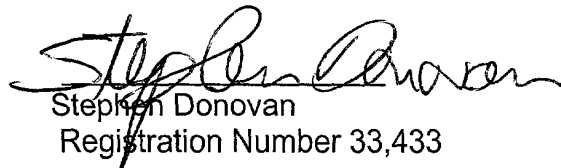
Thus, no new matter is introduced by any of the claim amendments or by any of the new claims.

#### V. Conclusion

Examination and allowance of the pending claims 1, 4 and 11-19 is requested.

Respectfully Submitted,

Date: March 15, 2001

  
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METHOD FOR TREATING NEUROMUSCULAR DISORDERS AND  
CONDITIONS WITH BOTULINUM TOXIN TYPES A AND B

CROSS REFERENCE

This application is a continuation of serial number  
08/075,048, filed June 10, 1993.

FIELD OF THE INVENTION

The present invention provides novel methods for treating diseases of the nervous system, e.g., neuromuscular disorders and conditions, with botulinum toxins. In addition, the present invention provides methods useful in all tissue and organ systems which involve the release of neurotransmitters, especially acetylcholine. These cholinergic transmission systems include neuromuscular junctions (muscles), smooth muscles (gut, sphincters, etc.) and secretions (salivation and mucus).

BACKGROUND OF THE INVENTION

A bacterial toxin, botulinum toxin, in particular botulinum toxin type A, has been used in the treatment of a number of neuromuscular disorders and conditions involving muscular spasm; for example, strabismus, blepharospasm, spasmodic torticollis (cervical dystonia), oromandibular dystonia and spasmodic dysphonia (laryngeal dystonia). The toxin binds rapidly and strongly to presynaptic cholinergic nerve terminals and inhibits the exocytosis of acetylcholine by decreasing the frequency of acetylcholine release. This results in local

paralysis and hence relaxation of the muscle afflicted by spasm.

For one example of treating neuromuscular disorders, see U.S. Patent No. 5,053,005 to Borodic, which suggests treating curvature of the juvenile

THE FOLLOWING TWO PAGES SHOWS A MARKED UP VERSION OF  
PAGE ONE OF THE SPECIFICATION

TREATMENT OF METHOD FOR TREATING NEUROMUSCULAR  
DISORDERS AND CONDITIONS WITH DIFFERENT BOTULINUM TOXIN  
TYPES A AND B SEROTYPE

CROSS REFERENCE

This application is a continuation of serial number  
08/075,048, filed June 10, 1993.

FIELD OF THE INVENTION

The present invention provides novel methods for treating diseases of the nervous system, e.g., neuromuscular disorders and conditions, with botulinum toxins. In addition, the present invention provides methods useful in all tissue and organ systems which involve the release of neurotransmitters, especially acetylcholine. These cholinergic transmission systems include neuromuscular junctions (muscles), smooth muscles (gut, sphincters, etc.) and secretions (salivation and mucus).

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**PLEASE REPLACE THE CLAIMS BY THE FOLLOWING UNMARKED  
VERSION OF THE CLAIMS**

1. A method of treating a patient suffering from a neuromuscular disorder or condition, said method comprising administering to the patient a therapeutically effective amount of a botulinum toxin type A until the patient experiences loss of clinical response to the administered botulinum toxin and thereafter administering to the patient a botulinum toxin type B, said botulinum toxin type B being administered in therapeutically effective amounts.

4. A method of treating a patient suffering from a neuromuscular disorder or condition, said method comprising administration to the patient of a therapeutically effective amount of a botulinum toxin type A until the patient develops neutralizing antibodies and thereafter administering to the patient a botulinum toxin type B, said botulinum toxin type B being administered in a therapeutically effective amount.

11. The method of claim 1 or 4, wherein the neuromuscular disorder or condition is cervical dystonia.

12. A method of treating dystonia in a patient, wherein the patient has experienced a loss of or a diminished clinical effectiveness to the administration of a botulinum toxin type A, said method comprising administering to the patient a therapeutically effective amount of a botulinum toxin type B.

13. The method of claim 12, wherein the dystonia is cervical dystonia

14. The method of claim 13, wherein treating the cervical dystonia reduces the severity of an abnormal head position symptom of the cervical dystonia.

15. The method of claim 13, wherein treating the cervical dystonia reduces a neck pain associated with the cervical dystonia.

16. A method of treating dystonia in a patient, wherein the patient has developed neutralizing antibodies to a botulinum toxin type A, said method comprising administering to the patient a therapeutically effective amount of a botulinum toxin type B.

17. The method of claim 16, wherein the dystonia is cervical dystonia

18. The method of claim 17, wherein treating the cervical dystonia reduces the severity of an abnormal head position symptom of the cervical dystonia.

19. The method of claim 17, wherein treating the cervical dystonia reduces a neck pain associated with the cervical dystonia.

## MARKED UP VERSION OF THE CLAIMS

1. A method of treating a patient suffering from a neuromuscular disorder or condition, said method comprising administering to the patient a therapeutically effective amount of a botulinum toxin type A ~~of a selected serotype~~ until the patient experiences loss of clinical response to the administered botulinum toxin and thereafter administering to the patient another a botulinum toxin type B ~~of a different serotype~~, said another botulinum toxin type B being administered in therapeutically effective amounts.

Cancel claim 2

Cancel claim 3

4. A method of treating a patient suffering from a neuromuscular disorder or condition, said method comprising administration to the patient of a therapeutically effective amount of a botulinum toxin type A ~~of a selected serotype~~ until the patient develops neutralizing antibodies and thereafter administering to the patient another a botulinum toxin type B ~~of a different serotype~~, said another botulinum toxin type B being administered in a therapeutically effective amount.

Cancel claims 5-10

Please add the following new claims 11-19:

11. The method of claim 1 or 4, wherein the neuromuscular disorder or condition is cervical dystonia.

12. A method of treating dystonia in a patient, wherein the patient has experienced a loss of or a diminished clinical effectiveness to the administration of a botulinum toxin type A, said method comprising administering to the patient a therapeutically effective amount of a botulinum toxin type B.

13. The method of claim 12, wherein the dystonia is cervical dystonia

14. The method of claim 13, wherein treating the cervical dystonia reduces the severity of an abnormal head position symptom of the cervical dystonia.

15. The method of claim 13, wherein treating the cervical dystonia reduces a neck pain associated with the cervical dystonia.

16. A method of treating dystonia in a patient, wherein the patient has developed neutralizing antibodies to a botulinum toxin type A, said method comprising administering to the patient a therapeutically effective amount of a botulinum toxin type B.

17. The method of claim 16, wherein the dystonia is cervical dystonia

18. The method of claim 17, wherein treating the cervical dystonia reduces the severity of an abnormal head position symptom of the cervical dystonia.

19. The method of claim 17, wherein treating the cervical dystonia reduces a neck pain associated with the cervical dystonia.